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论著

缬沙坦对阿霉素心肌病大鼠的心脏保护作用及机制研究

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摘要 目的: 探讨AT1受体阻滞剂缬沙坦对阿霉素心肌病(ADR-DCM)大鼠的心脏保护作用及其机制。
方法: 雄性Wistar大鼠分3组: (1)阿霉素心肌病组(ADR-DCM, n=25), 阿霉素 2.5 mg/kg , 尾静脉注射, 每周1次, 连续10周; (2)阿霉素心肌病+缬沙坦治疗组(ARB, n=10), 缬沙坦 30 mg/kg , 每天1次, 灌胃治疗; (3)正常对照组(CON, n=10)。12周时进行超声和血流动力学检测, 氯胺T法检测羟脯氨酸及胶原含量, Western印迹分析检测MMP-2、MMP-9及TIMP-1的表达, 明胶酶谱法检测MMPs活性。
结果: ARB组死亡率明显低于ADR-DCM组(20% vs 40%, P<0.01)。ADR-DCM组大鼠左室内径大于CON组, 心功能明显低于CON组, ARB组左室内径增加程度及心功能各项指标变化低于ADR-DCM组。ADR-DCM组心肌羟脯氨酸及胶原含量高于CON组, ARB组显著低于ADR-DCM组(P<0.01)。ADR-DCM组左室心肌MMP-2、MMP-9蛋白表达及MMPs明胶酶活性明显高于CON组 (P<0.01), ARB组MMP-2、MMP-9表达及活性明显低于ADR-DCM组(P<0.01), 而TIMP-1的表达在3组间均无显著差异(P>0.05)。
结论: 缬沙坦部分通过抑制MMPs表达及活性逆转ADR-DCM左室重构, 改善心功能。

关键词 多柔比星 心肌疾病; 基质金属蛋白酶; 缬沙坦; 受体,血管紧张素
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Valsartan protects a rat model of adriamycin-induced dilated cardiomyopathy from left ventricular remodeling and failure

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Abstract

<FONT face=Verdana>AIM: To investigate whether and how AT1 receptor blocker, valsartan, attenuates left ventricular remodeling and failure in a rat model of adriamycin (ADR)-induced dilated cardiomyopathy.
METHODS: Weight-matched adult male Wistar rats were randomly divided into 3 groups as follows: 1) the ADR group, in which 2.5 mg/kg of ADR was weekly injected via a tail vein for 10 weeks (n=25); 2) concomitant AT 1 receptor blocker valsartan and ADR, in which valsartan was administered by daily gavage at a dose of 30 mg·kg -1 ·d -1 (n=10); 3) control group (n=10). Hemodynamics and echocardiographic measurements were obtained at 12 weeks after treatment. Finally, left ventricle (LV) samples were collected at 12 weeks. The hydroxyproline content was determined by the methods of chloramines T. The expression of MMP-2, MMP-9 and tissue inhibitors of metalloproteinase-1 (TIMP-1) were measured by Western blotting. MMP-2 and -9 gelatinolytic activities were measured by gelatin zymography.
RESULTS: Mortality was significantly lower in valsartan -treated rats than that in ADR rats (20% versus 40%, P<0.01). The dilatation of LV cavity was significantly attenuated in ADR-induced dilated cardiomyopathy rats given valsartan. Valsartan partially normalized LV contractile function, which was significantly reduced in ADR rats. The hydroxyproline content was increased in ADR-DCM group and significantly reduced by valsartan treatment (P<0.01). The protein levels of LV MMP-2 and MMP-9 were increased in ADR rats and attenuated by valsartan treatment (both P<0.01). However, no change in TIMP-1 was observed (P>0.05). The activities of LV myocardial MMP-2 and -9 gelatinolytic were increased significantly in ADR rats (both P<0.01) and attenuated by valsartan treatment (both P<0.01).
CONCLUSION: Pretreatment with AT 1 receptor blocker valsartan

attenuates left ventricular remodeling and failure in a rat model of adriamycin-induced dilated cardiomyopathy.</FONT>

Key words Doxorubicin Myocaridial diseases Matrix metalloproteinases Valsartan Receptors angiotensin

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